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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Indole Derivatives

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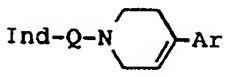
Abstract of the Disclosure

Indole derivatives of formula I



I

nwherein Ind, Q and Ar are as defined in Claim 1, and their salts, are active on the central nervous system.

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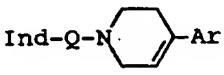
Indole derivatives

The invention relates to novel indole derivatives of formula I



I

wherein
Ind is an indol-3-yl radical substituted by $-O-CH_2-CO-R^1$, $-NHR^2$, $-NO_2$, $-CO-NR^3R^4$ or $-CSNH_2$,
R^1 is OH, OA, NH_2, NHA, NA_2, $NH-CH_2COOA$ or $NHCH(CH_2OH)COOA$,
R^2 is H, Ac, $CONH_2$, CONHA, $CONA_2$ or SO_2A,
R^3 is H, A or hydroxyalkyl,
R^4 is hydroxyalkyl, AO-alkyl, AcO-alkyl, ANH-CO-O-alkyl, AOOC-alkyl, H_2NCO-alkyl, HSO_3-alkyl, A_2N-alkyl, Ar, Ar-alkyl or Het-alkyl,
R^3 and R^4 together are also an alkylene group having 3-7 C atoms, which can be interrupted by O or NR^5 and/or substituted by NA_2, NHAc, COOA, $CONH_2$, Ar or Het, and/or can contain an additional double bond,
R^5 is H, A, Ar, Het, Ac, COOA, CH_2CONH_2, CH_2CONHA, CH_2CONA_2 or CH_2CONR^6,
R^6 is alkylene having 3-7 C atoms,
Q is $-(CH_2)_n-$, $-CH_2-S-CH_2CH_2-$, $-CH_2-SO-CH_2CH_2-$ or $-CH_2-SO_2-CH_2CH_2-$,
n is 2, 3, 4 or 5,
A is alkyl having 1-4 C atoms,
-alkyl- is alkylene having 1-4 C atoms,
Ar is a phenyl group which is unsubstituted, monosubstituted or disubstituted by F, Cl, Br, OA and/or OH or substituted by a methylenedioxy group, or a thien-2-yl or thien-3-yl group,
Ac is A-CO- or Ar-CO- and

Het is a saturated or unsaturated 5-membered or 6-membered heterocyclic radical having 1-4 N, O and/or S atoms, which can be fused with a benzene ring and/or monosubstituted or disubstituted by A,

and to their salts.

The object of the invention was to find novel compounds capable of being used for the preparation of drugs.

It has been found that the compounds of formula I and their biocompatible acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially as dopamine stimulants (parkinsonism inhibitors) and as serotonin agonists and antagonists. Specifically, the compounds of formula I induce contralateral rotational behaviour in rats suffering from parkinsonism on one side (this can be established by the method of Ungerstedt et al., Brain Res. 24 (1970), 485-493). They inhibit the binding of tritiated dopamine agonists and antagonists to extrapyramidal receptors (this can be established by the method of Schwarcz et al., J. Neurochemistry 34 (1980), 772-778, and Creese et al., European J. Pharmacol. 46 (1977), 377-381) and the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol. 140 (1987), 143-155). They also modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphes (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41). In addition, the compounds inhibit the linguomandibular reflex in narcotized rats (this can be established on the basis of the methods of Barnett et al., European J. Pharmacol. 21 (1973), 178-182, and von Ilhan et al., European J. Pharmacol. 33 (1975), 61-64). They also have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646-648), the directly measured blood pressure is lowered after oral administration of the compounds.

Compounds of formula I and their biocompatible acid addition salts can therefore be used as active ingredients for anxiolytics, antidepressants, neuroleptics, parkinsonism inhibitors and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

The invention relates to the indole derivatives of formula I and to their biocompatible acid addition salts.

The radical A is alkyl having 1, 2, 3 or 4 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl. OA is preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert-butylamino. NA_2 is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

Analogously, $NH-CH_2COOA$ is preferably methoxycarbonylmethylamino or ethoxycarbonylmethylamino; $NHCH(CH_2OH)COOA$ is preferably 1-methoxycarbonyl-2-hydroxyethylamino or 1-ethoxycarbonyl-2-hydroxyethylamino; CONHA is preferably N-methylcarbamoyl or N-ethylcarbamoyl; $CONA_2$ is preferably N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl; CS-NH-COOA is preferably methoxycarbonylaminothioxo or ethoxycarbonylaminothioxo; SO_2A is preferably methylsulphonyl or ethylsulphonyl; COOA is preferably methoxycarbonyl or ethoxycarbonyl; CH_2CONHA is preferably N-methylcarbamoylmethyl or N-ethylcarbamoylmethyl; and CH_2CONA_2 is preferably N,N-dimethylcarbamoylmethyl or N,N-diethylcarbamoylmethyl.

The group -alkyl- is a linear or branched alkylene group having especially 1 or 2 C atoms, preferably $-CH_2-$ or $-CH_2CH_2-$, but also e.g. $-CH(CH_3)-$, $-(CH_2)_3-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2-$ or $-(CH_2)_4-$.

Accordingly, hydroxyalkyl is preferably hydroxymethyl or 1- or 2-hydroxyethyl, other preferred meanings

being 3-hydroxypropyl, 4-hydroxybutyl or 2-hydroxy-1,1-dimethylethyl; AO-alkyl is preferably methoxymethyl, ethoxymethyl, 1- or 2-methoxyethyl or 1- or 2-ethoxyethyl; ANH-CO-O-alkyl is preferably N-methylcarbamoyloxymethyl, N-ethylcarbamoyloxymethyl, 1- or 2-(N-methylcarbamoyloxy)ethyl or 1- or 2-(N-ethylcarbamoyloxy)ethyl; AOOC-alkyl is preferably methoxycarbonylmethyl, ethoxycarbonylmethyl, 1- or 2-methoxycarbonylethyl or 1- or 2-ethoxycarbonylethyl; H_2N-CO-alkyl is preferably carbamoylmethyl or 1- or 2-carbamoylethyl; HSO_3-alkyl is preferably sulphomethyl or 1- or 2-sulphoethyl; and A_2N-alkyl is preferably dimethylaminomethyl, diethylaminomethyl, 1- or 2-dimethylaminoethyl or 1- or 2-diethylaminoethyl.

The radical Ar is preferably unsubstituted phenyl. If Ar is a substituted phenyl group, it is preferably monosubstituted. However, it can also be disubstituted, it being possible for the substituents to be identical or different. Preferred substituents on the phenyl group are F, Cl, methoxy or OH. Specifically, Ar is preferably phenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-methoxyphenyl or o-, m- or p-hydroxyphenyl, and also o-, m- or p-bromophenyl, o-, m- or p-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 3-hydroxy-4-methoxyphenyl, 3-methoxy-4-hydroxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dihydroxyphenyl, 2,3- or 3,4-methylenedioxyphenyl, thien-2-yl or thien-3-yl.

Accordingly, Ar-alkyl is preferably benzyl, 1- or 2-phenylethyl, o-, m- or p-fluorobenzyl, o-, m- or p-chlorobenzyl, o-, m- or p-methoxybenzyl, 1- or 2-o-, -m- or -p-methoxyphenylethyl, o-, m- or p-hydroxybenzyl or 1- or 2-o-, -m- or -p-hydroxyphenylethyl.

Ac is preferably acetyl or benzoyl, other preferred meanings being propionyl, butyryl, isobutyryl, o-, m- or p-fluorobenzoyl, o-, m- or p-chlorobenzoyl, o-, m- or p-hydroxybenzoyl or o-, m- or p-methoxybenzoyl. Accordingly, AcO-alkyl is preferably acetoxymethyl, 1- or 2-acetoxyethyl, benzoyloxymethyl or 1- or 2-benzoyloxy-

ethyl; NHAc is preferably acetamido or benzamido.

Het is preferably furan-2-yl or furan-3-yl, thien-2-yl or thien-3-yl, pyrrol-1-, -2- or -3-yl, imidazol-1-, -2-, -4- or -5-yl, pyrazol-1-, -3-, -4- or -5-yl, oxazol-2-, -4- or -5-yl, isoxazol-3-, -4- or -5-yl, thiazol-2-, -4- or -5-yl, isothiazol-3-, -4- or -5-yl, pyrid-2-, -3- or -4-yl or pyrimidin-2-, -4-, -5- or -6-yl, other preferred meanings being 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, tetrazol-1- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2H-thiopyran-2-, -3-, -4-, -5- or -6-yl, 4H-thiopyran-2-, -3- or -4-yl, pyridazin-3- or -4-yl, pyrazinyl, benzofuran-2-, -3-, -4-, -5-, -6- or -7-yl, benzothien-2-, -3-, -4-, -5-, -6- or -7-yl, indol-1-, -2-, -3-, -4-, -5-, -6- or -7-yl, isoindol-1-, -2-, -3-, -4-, -5-, -6- or -7-yl, benzimidazol-1-, -2-, -4- or -5-yl, benzopyrazol-1-, -3-, -4-, -5-, -6- or -7-yl, benzoxazol-2-, -4-, -5-, -6- or -7-yl, benzisoxazol-3-, -4-, -5-, -6- or -7-yl, benzthiazol-2-, -4-, -5-, -6- or -7-yl, benzisothiazol-2-, -4-, -5-, -6- or -7-yl, benz-2,1,3-oxadiazol-4-, -5-, -6- or -7-yl, quinol-2-, -3-, -4-, -5-, -6-, -7- or -8-yl, isoquinol-1-, -3-, -4-, -5-, -6-, -7- or -8-yl, carbazol-1-, -2-, -3-, -4- or -9-yl, acridin-1-, -2-, -3-, -4-, -5-, -6-, -7-, -8- or -9-yl, cinnol-3-, -4-, -5-, -6-, -7- or -8-yl or quinazol-2-, -4-, -5-, -6-, -7- or -8-yl. The heterocyclic radicals can also be partially or completely hydrogenated. Het can therefore also be e.g. 2,3-dihydrofuran-2-, -3-, -4- or -5-yl, 2,5-dihydrofuran-2-, -3-, -4- or -5-yl, tetrahydrofuran-2- or -3-yl, tetrahydrothien-2- or -3-yl, 2,3-dihydropyrrol-1-, -2-, -3-, -4- or -5-yl, 2,5-dihydropyrrol-1-, -2-, -3-, -4- or -5-yl, pyrrolidin-1-, -2- or -3-yl, tetrahydroimidazol-1-, -2- or -4-yl, 2,3-dihydropyrazol-1-, -2-, -3-, -4- or -5-yl, tetrahydropyrazol-1-, -3- or -4-yl, 1,4-dihydropyrid-1-, -2-, -3- or -4-yl, 1,2,3,4-tetrahydropyrid-1-, -2-, -3-, -4-, -5- or -6-yl, 1,2,3,6-tetrahydropyrid-1-, -2-, -3-, -4-, -5- or -6-yl,

piperidin-1-, -2-, -3- or -4-yl, morpholin-2-, -3- or -4-yl, tetrahydropyran-2-, -3- or -4-yl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydropyridazin-1-, -3- or -4-yl, hexahydropyrimidin-1-, -2-, -4- or -5-yl, piperazin-1-, -2- or -3-yl, 1,2,3,4-tetrahydroquinol-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-yl or 1,2,3,4-tetrahydroisoquinol-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-yl.

The heterocyclic radicals can also be substituted as indicated. Het can preferably also be e.g. 4- or 5-methylthiazol-2-yl, 4-, 5- or 6-methylpyrimidin-2-yl, 4,5-dimethylthiazol-2-yl, 3-, 4- or 5-methylfuran-2-yl, 2-, 4- or 5-methylfuran-3-yl, 2,4-dimethylfuran-3-yl, 3-, 4- or 5-methylthien-2-yl, 2-, 4- or 5-methylthien-3-yl or 3-methyl-5-tert-butylthien-2-yl.

The radical Ind is an indol-3-yl radical monosubstituted by one of the radicals indicated. It is preferably substituted in the 5-position or else in the 4-, 6- or 7-position. Substitution in the 1- or 2-position is a further possibility. Preferred substituents on the indol-3-yl radical are $-NHR^2$, $-NO_2$ and $-CONR^3R^4$.

R^1 is preferably OH, NH_2, NA_2, $NHCH_2COOA$ or $NHCH(CH_2OH)COOA$.

R^2 is preferably $CONH_2$, other preferred meanings being H, Ac or SO_2A.

R^3 is preferably H.

R^4 is preferably hydroxyalkyl, other preferred meanings being AOOC-alkyl, H_2NCO-alkyl, A_2N-alkyl, Ar or HSO_3-alkyl.

The group $-NR^3R^4$ is preferably also pyrrolidino, piperidino, morpholino, 4-R^5-piperazino or 4-R^7-piperidino, R^5 preferably being H, A, Ar, pyrimidin-2-yl, 5-methylthiazolyl, Ar-CO, COOA, CH_2CONHA or pyrrolidinocarbonylmethyl and R^7 preferably being NA_2, NHCOAr, COOA, $CONH_2$, piperidino or morpholino, or else NHCOA, Ar or another Het group.

The parameter n is preferably 4 and the radical Q is preferably $-(CH_2)_4-$ or $-CH_2S-CH_2CH_2-$, or else $-CH_2-SO-CH_2CH_2-$, $-CH_2-SO_2-CH_2CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-(CH_2)_5-$.

Accordingly, the invention relates particularly to those compounds of formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to If, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, Ind is an indol-3-yl radical substituted in the 5-position by $-O-CH_2-CO-R^1$;

in Ib, Ind is an indol-3-yl radical substituted in the 5-position by $-NHR^3$;

in Ic, Ind is a 5-nitroindol-3-yl radical;

in Id, Ind is an indol-3-yl radical substituted in the 5-position by $-CONR^3R^4$;

in Ie, Ind is an indol-3-yl radical substituted in the 5-position by $-CSNH_2$; and

in If, Ind is a 5-ureidoindol-3-yl radical.

Especially preferred compounds are those of partial formulae Ig and Iag to Ifg, which correspond to partial formulae I and Ia to If, but in which additionally:

Q is $-(CH_2)_4-$.

Other especially preferred compounds are those of partial formulae Ih, Iah to Ifh, Igh and Iagh to Ifgh, which correspond to partial formulae I, Ia to If, Ig and Iag to Ifg, but in which additionally:

Ar is phenyl.

The invention further relates to a process for the preparation of indole derivatives of formula I and their salts, characterized in that a compound of formula II

$$Ind-Q-X^1 \qquad II$$

wherein

X^1 is X or NH_2,

X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and

Ind and Q are as defined,
is reacted with a compound of formula III

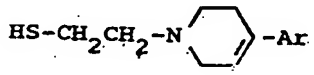
$$X^2\text{-}CH_2CH_2CAr{=}CH\text{-}CH_2X^3 \qquad III$$

wherein
X^2 and X^3 can be identical or different and are each X if $X^1 = NH_2$ or are together NH in other cases, and
Ar is as defined,
or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds is treated with a reducing agent,
or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolyzable groups is treated with a solvolyzing agent,
or in that, to prepare thioethers of formula I in which Q is $-CH_2-S-CH_2CH_2-$, a compound of formula IV

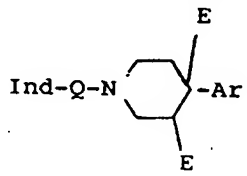
$$Ind\text{-}CH_2N(R)_2 \qquad IV$$

wherein
R is alkyl having 1-4 C atoms or else both radicals R together are $-(CH_2)_p-$ or $-CH_2CH_2OCH_2CH_2-$,
p is 4 or 5 and
Ind is as defined,
is reacted with a thiol of formula V

V



wherein
Ar is as defined,
or with one of its reactive derivatives,
or in that a compound of formula VI



VI

wherein
one of the radicals E is X, CN or NH_2,
the other radical E is H and
Ind, Q, Ar and X are as defined,
is treated with an agent which eliminates HE,
or in that, to prepare a compound of formula I in which Ind is an indol-3-yl radical substituted by $-O-CH_2-CO-R^1$, a hydroxyindole which has formula I except that Ind has been replaced by an indol-3-yl radical substituted by an OH group, or one of its reactive derivatives, is reacted with a compound of the formula $X-CH_2-CO-R^1$ (wherein X and R^1 are as defined),
or in that, to prepare a compound of formula I in which Ind is an indol-3-yl radical substituted by $-CO-NR^3R^4$, an indolecarboxylic acid which has formula I except that Ind has been replaced by an indol-3-yl radical substituted by a COOH group, or one of its reactive derivatives, is reacted with a compound of the formula HNR^3R^4 (wherein R^3 and R^4 are as defined),
or in that, to prepare a compound of formula I in which Ind is an indol-3-yl radical substituted by $-CS-NH_2$, a cyanoindole which has formula I except that Ind has been replaced by an indol-3-yl radical substituted by a CN group is reacted with H_2S or an agent which releases H_2S,
and/or in that, if desired, in a compound of formula I, a thioether group is oxidized to an SO group or SO_2 group or an SO group is oxidized to an SO_2 group, and/or an OA group is cleaved to form an OH group, and/or an Ind group is converted into another Ind group, and/or in that a resulting base of formula I is converted into one of its salts by treatment with an acid or base.

The compounds of formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; German Offen-

legungsschrift 33 42 632), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of formula I.

In the indole derivatives of formula II, X^1 is preferably X; accordingly, in the compounds of formula III, X^2 and X^3 are together preferably NH. The radical X is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulphonyloxy having 1-6 C atoms (e.g. methanesulphonyloxy) or arylsulphonyloxy having 6-10 C atoms (e.g. benzenesulphonyloxy, p-toluenesulphonyloxy, naphthalene-1- or -2-sulphonyloxy).

Accordingly, the indole derivatives of formula I can be obtained especially by reacting compounds of the formula Ind-Q-Cl or Ind-Q-Br with tetrahydropyridine derivatives of formula III in which X^2 and X^3 together are an NH group (designated as IIIa hereafter).

Some of the compounds of formulae II and, in particular, III are known; the unknown compounds of formulae II and III can easily be prepared analogously to the known compounds. Compounds of formula II (Q = $-CH_2-S-CH_2CH_2-$) can be prepared e.g. from Mannich bases of formula IV and thiols of the formula $HS-CH_2CH_2-X^1$, e.g. $HS-CH_2CH_2OH$. The sulphoxides and sulphones of formula II (Q = $-CH_2-SO-CH_2CH_2-$ or $-CH_2-SO_2-CH_2CH_2-$) are accessible by oxidation of the thioethers (II, Q = $-CH_2-S-CH_2CH_2-$). Primary alcohols of the formula Ind-Q- OH can be obtained e.g. by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar halogen compounds yields the corresponding halides of the formula Ind-Q-Hal. The corresponding sulphonyloxy compounds can

be obtained from the alcohols Ind-Q-OH by reaction with the appropriate sulphonyl chlorides.

The iodine compounds of the formula Ind-Q-I can be obtained e.g. by reacting potassium iodide with the appropriate p-toluenesulphonic acid esters. The amines of the formula Ind-Q-NH_2 can be prepared e.g. from the halides with potassium phthalimide or by reducing the appropriate nitriles.

Most of the piperidine derivatives IIIa are known (q.v. German Offenlegungsschrift 20 60 816) and can be obtained e.g. by reacting piperid-4-one with organometallic compounds of the formula M-Ar (wherein M is an Li atom or MgHal), this being followed by hydrolysis to give the corresponding 4-Ar-4-hydroxypiperidines and, if desired, by dehydration to give 4-Ar-3,4-dehydropiperidines. Compounds of formula III (X^2 and X^3 = X in each case) can be prepared e.g. by reducing diesters of the formula alkylOOC-CH_2-CAr=CH-COOalkyl to give diols of the formula HO-CH_2CH_2-CAr=CH-CH_2OH (III, X^2 = X^3 = OH), this being followed, if desired, by reaction with $SOCl_2$ or PBr_3.

The reaction of the compounds II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favourable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium,

sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component Ind-Q-NH_2 or of the piperidine derivative of formula IIIa. The reaction time is between a few minutes and 14 days, depending on the conditions used, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

A compound of formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds, with a reducing agent, preferably at temperatures of between -80 and +250°, in the presence of at least one inert solvent.

Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulphonyloxy (e.g. p-toluenesulphonyloxy), N-benzenesulphonyl, N-benzyl or O-benzyl.

In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of formula I by reduction, it being possible simultaneously to reduce substituents in the Ind group which are present in the starting compound. This is preferably carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction.

Preferred starting materials for the reduction have formula VII

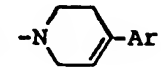
Ind'-L-W VII

wherein

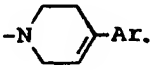
Ind' is an Ind radical which can additionally be substituted in the 1-position by an arylsulphonyl group or a benzyl group,

L is Q or a chain which corresponds to the radical Q except that one or more -CH_2- groups have been replaced by -CO- groups and/or one or more hydrogen atoms have been

replaced by OH groups,

W is  or  ;

$An^{\ominus}$ is an anion of a strong acid and
Ar' is a phenyl group which is unsubstituted, monosubstituted or disubstituted by F, Cl, Br, OA, OH and/or O-benzyl or substituted by a methylenedioxy group,
but wherein the following meanings cannot apply simultaneously: Ind' = Ind, L = Q and

W =  .

In the compounds of formula VII, L is preferably $-CO-(CH_2)_{n-2}-CO-$ [specifically $-COCO-$, $-COCH_2CO-$, $-CO-(CH_2)_2-CO-$, $-CO-(CH_2)_3-CO-$], $-(CH_2)_{n-1}-CO-$ [specifically $-CH_2CO-$, $-CH_2CH_2-CO-$, $-(CH_2)_3-CO-$ or $-(CH_2)_4-CO-$], $-CH_2-S-CH_2-CO-$, $-CH_2-SO-CH_2-CO-$ or $-CH_2-SO_2-CH_2-CO-$, further examples being $-CO-CH_2CH_2-$, $-CH_2-CO-CH_2-$, $-CO-(CH_2)_3-$, $-CH_2-CO-CH_2CH_2-$, $-CH_2CH_2-CO-CH_2-$, $-CO-(CH_2)_4-$, $-CH_2-CO-(CH_2)_3-$, $-CH_2CH_2-CO-CH_2CH_2-$ or $-(CH_2)_3-CO-CH_2-$.

Compounds of formula VII can be prepared e.g. by reacting 4-Ar'-1,2,3,6-tetrahydropyridine or 4-Ar'-pyridine with a compound of formula VIII

$$Ind'-L-X^1 \qquad VIII$$

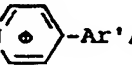
wherein
Ar', Ind', L and X^1 are as defined above,
under the conditions indicated above for the reaction of II with III.

If nascent hydrogen is used as the reducing agent, this can be produced e.g. by treating metals with weak acids or with bases. Thus it is possible e.g. to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an

aluminium-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminium amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

Other reducing agents which can be used to particular advantage are complex metal hydrides such as $LiAlH_4$, $NaBH_4$, diisobutylaluminium hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$, and diborane, catalysts such as BF_3, $AlCl_3$ or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for reduction with $NaBH_4$ are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of between -80 and +150°, especially of between about 0 and about 100°.

The reduction of -CO- groups in acid amides (e.g. those of formula VII in which L is a $-(CH_2)_{n-1}-CO-$ or $-CH_2-S-CH_2-CO-$ group) to $-CH_2-$ groups can be carried out to particular advantage with $LiAlH_4$ in THF at temperatures of between about 0 and 66°. Arylsulphonyl protecting groups located in the 1-position of the indole ring can be simultaneously eliminated by reduction.

Reduction of the pyridinium salts of formula VII (wherein W is  -Ar'$An^{\ominus}$ and An is preferably Cl, Br or CH_3SO_3) to compounds of formula I is carried out e.g. with $NaBH_4$ in water, methanol or ethanol or in mixtures of these solvents, a base such as NaOH being added if desired, at temperatures of between about 0 and 80°.

N-Benzyl groups can be eliminated by reduction with sodium in liquid ammonia.

It is also possible to reduce one or more car-

bonyl groups to CH_2 groups according to the Wolff-Kishner method, e.g. by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of between about 150 and 250°. A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 3-4 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200°. The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulphoxide at room temperature.

Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolyzable groups can be solvolyzed, especially hydrolyzed, to give the compounds of formula I.

The starting materials for the solvolysis can be obtained for example by reacting IIIa with compounds which have formula II (X^1 = X) except that one or more H atoms have been replaced by one or more solvolyzable groups. Thus, in particular, 1-acylindole derivatives (which have formula I except that, in the 1-position of the Ind radical, they contain an acyl group, preferably an alkanoyl, alkylsulphonyl or arylsulphonyl group having up to 10 C atoms in each case, such as methanesulphonyl, benzenesulphonyl or p-toluenesulphonyl) can be hydrolyzed to give the corresponding indole derivatives unsubstituted in the 1-position of the indole ring, e.g. in an acidic or, preferably, neutral or alkaline medium at temperatures of between 0 and 200°. Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulphones such as tetramethylenesulphone; or mixtures thereof, especially mixtures containing water. Hydroly-

sis can also be carried out simply by treatment with water alone, especially at the boiling point.

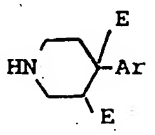
Indole derivatives of formula I (Q = $-CH_2-S-CH_2CH_2-$) can also be obtained by reacting Mannich bases of formula IV with thiols of formula V or their salts or reactive derivatives.

Some of the starting materials of formulae IV and V are known; those which are not known can easily be prepared analogously to the known compounds. Thus the Mannich bases of formula IV can be obtained e.g. from indoles of the formula Ind-H, formaldehyde and amines of the formula $HN(R)_2$ and the thiols of formula V can be obtained from the bases of formula IIIa and thiol derivatives of the formula $HS-CH_2CH_2-X^1$ (it also being possible for the HS group to be protected in an intermediate step).

Specifically, the reaction of IV with V takes place in the presence or absence of an inert solvent, at temperatures of between about -20 and 250°, preferably of between 60 and 150°. Examples of suitable solvents are hydrocarbons such as benzene, toluene, xylenes or mesitylene; tertiary bases such as triethylamine, pyridine or picoline; alcohols such as methanol, ethanol or butanol; glycols and glycol ethers such as ethylene glycol, diethylene glycol or 2-methoxyethanol; ketones such as acetone; ethers such as THF or dioxane; amides such as DMF; and sulphoxides such as dimethyl sulphoxide. Mixtures of these solvents are also suitable. The thiols of formula V are conveniently converted first into the corresponding mercaptides, preferably by reaction with sodium or potassium hydroxide or sodium or potassium ethylate to give the corresponding sodium or potassium mercaptides. Reactive derivatives of the thiols of formula V which can be used are preferably the corresponding isothioureas (which have formula V except that HS- has been replaced by $H_2N(=NH)-S-$) or their salts (e.g. the isothiuronium chlorides); these are more stable and easier to handle. Their reaction with the bases IV is conveniently carried out in a basic medium, e.g. in

aqueous sodium hydroxide solution, at temperatures of between 0 and 100°.

Compounds of formula I are also obtained by eliminating HE from compounds of formula VI to form a double bond. According to the definition of E, the molecule eliminated can be e.g. a hydrogen halide, water (dehydration), a carboxylic acid or other acid, ammonia or HCN. The starting materials of formula VI can be obtained e.g. by reacting II (X^1 = X) with a compound of formula IX



IX

wherein E and Ar are as defined.

If one of the radicals E = Hal, this substituent can easily be eliminated under basic reaction conditions. The following bases can be used: alkali metal hydroxides, alkali metal carbonates, alcoholates such as potassium tert-butylate, and amines such as dimethylaniline, pyridine, collidine or quinoline; examples of solvents used are benzene, toluene, cyclohexane, THF or tert-butanol. The amines serving as bases can also be used in excess as solvents. If one of the radicals E is an OH group, acids such as acetic acid, hydrochloric acid or mixtures of both are preferably used as water-eliminating agents. It may be advantageous to add a solvent (e.g. water or ethanol). The elimination of acyloxy, alkylsulphonyloxy and alkoxysulphonyloxy radicals or amino radicals can be carried out under similar conditions. The elimination of sulphonic acid radicals, e.g. those of mesylates or tosylates, is carried out under mild conditions by boiling in DMF or dimethyl sulphoxide with alkali metal carbonates, e.g. Li_2CO_3, or with potassium acetate. Ammonia can be eliminated simply by heating the salts of the corresponding amino compounds (especially the 4-amino derivatives). Similarly, HCN can be eliminated from compounds of formula VI (one group E = CN) by

heating. In general, HE is eliminated from VI at temperatures of between 0 and about 250°, preferably of between 50 and 200°.

Compounds of formula I in which Ind is an indol-3-yl radical substituted by $-O-CH_2-CO-R^1$ can be obtained by etherifying appropriate hydroxyindol-3-yl compounds (q.v. European patent 7399) or their reactive derivatives, in particular their salts, e.g. their alkali metal salts such as their Na or K salts, with compounds of the formula $X-CH_2-CO-R^1$ (e.g. chloroacetic or bromoacetic acid, methyl or ethyl chloroacetate or bromoacetate, chloroacetamide or bromoacetamide, chloro-N-methylacetamide or bromo-N-methylacetamide, chloro-N,N-dimethylacetamide or bromo-N,N-dimethylacetamide). The etherification reaction is conveniently carried out in one of the solvents indicated (e.g. DMF), the hydroxyl compound first being converted into one of its salts with the aid of a base, e.g. an alkali metal hydride such as NaH or KH, or an alkali metal alcoholate such as sodium or potassium methylate or ethylate, after which the compound of the formula $X-CH_2-CO-R^1$ is added and the mixture is stirred for a few hours at temperatures of between 0 and 150°, preferably of between 20 and 80°.

Compounds of formula I in which Ind is an indol-3-yl radical substituted by $-CO-NR^3R^4$ can be obtained by amidating appropriate carboxyindol-3-yl compounds (q.v. German Offenlegungsschrift 33 42 632) or their reactive derivatives, e.g. their acid halides, esters or anhydrides, with amines of the formula HNR^3R^4. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g. a carbodiimide such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphorylazide or 2- ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, e.g. a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or

dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of between about -10 and 40, preferably of between 0 and 30°. Instead of the acid or amide, it is also possible to use reactive derivatives of these substances in the reaction, e.g. those in which reactive groups are blocked by protecting groups in an intermediate step. The acids can also be used in the form of their activated esters, which are conveniently formed in situ, e.g. by the addition of 1-hydroxybenztriazole or N-hydroxysuccinimide.

Compounds of formula I in which Ind is an indol-3-yl radical substituted by $-CS-NH_2$ can be obtained by adding H_2S on to appropriate cyanoindol-3-yl compounds. Agents which release H_2S, e.g. thioacetamide, can also be used instead of H_2S. The reaction is conveniently carried out in one of the solvents indicated, e.g. DMF, in the presence of an acid, e.g. HCl, at temperatures of between 0 and 200, preferably of between 20 and 160°.

Furthermore, one compound of formula I can be converted into another compound of formula I by methods known per se.

Thus the thioether group in a thioether of formula I (Q = $-CH_2-S-CH_2CH_2-$) can be oxidized to an SO group or to an SO_2 group, or the SO group in a sulphoxide of formula I (Q = $-CH_2-SO-CH_2CH_2-$) can be oxidized to an SO_2 group. If it is desired to obtain the sulphoxides, oxidation is carried out for example with hydrogen peroxide, peracids such as m-chloroperbenzoic acid, Cr(VI) compounds such as chromic acid, $KMnO_4$, 1-chlorobenztriazole, Ce(IV) compounds such as $(NH_4)_2Ce(NO_3)_6$, or negatively substituted aromatic diazonium salts such as o- or p-nitrophenyldiazonium chloride, or by electrolysis under relatively mild conditions and at relatively low temperatures (about -80 to +100°). If, on the other hand, it is desired to obtain the sulphones (from the thioethers or the sulphoxides), the same oxidizing agents are used under more vigorous conditions and/or in excess, and normally at higher temperatures. The customary inert solvents may be present or absent in these reactions.

Examples of suitable inert solvents are water, aqueous mineral acids, aqueous alkali metal hydroxide solutions, lower alcohols such as methanol or ethanol, esters such as ethyl acetate, ketones such as acetone, lower carboxylic acids such as acetic acid, nitriles such as acetonitrile, hydrocarbons such as benzene, and chlorinated hydrocarbons such as chloroform or CCl_4. A preferred oxidizing agent is 30% aqueous hydrogen peroxide. This yields the sulphoxides if the calculated amount is used in solvents such as acetic acid, acetone, methanol, ethanol or aqueous sodium hydroxide solution, at temperatures of between -20 and 100°, and to the sulphones if an excess is used at higher temperatures, preferably in acetic acid or in a mixture of acetic acid and acetic anhydride.

Ethers of formula I in which the radical Ar is monosubstituted or disubstituted by O-alkyl can be cleaved to form the corresponding hydroxyl derivatives. For example, the ethers can be cleaved by treatment with dimethyl sulphide/boron tribromide complex, e.g. in toluene, ethers such as THF, or dimethyl sulphoxide, or by melting with pyridine hydrohalides or aniline hydrohalides, preferably pyridine hydrochloride, at about 150-250°.

Furthermore, Ind groups can be converted into other Ind groups by methods known per se. Carboxyl groups can be esterified, e.g. by treatment with alcohols in the presence of acid catalysts, or by reaction with diazoalkanes. Conversion of the carboxylic acids into their chlorides, e.g. with $SOCl_2$, and subsequent reaction with NH_3 or amines yields the corresponding carboxamides, which can also be obtained by treating the carboxylic acid esters with ammonia or amines. Solvolysis, preferably hydrolysis under the conditions indicated above, yields the carboxylic acids from the esters or amides; in particular, carboxylic acids can be obtained from the esters by treating the latter with NaOH or KOH in aqueous alcohols, conveniently at temperatures of between about 50 and about 200°. The reduction of nitro groups to

amino groups is carried out e.g. with metals such as Fe, Sn or Zn, or with $SnCl_2$, conveniently in aqueous- alcoholic acids, e.g. in aqueous-ethanolic hydrochloric acid, at temperatures of between 20 and 100°. Hydroxyl groups or amino groups can be acylated, e.g. with acid chlorides such as acetyl chloride, benzoyl chloride or methanesulphonyl chloride, in the presence of a base such as triethylamine or pyridine, and in the presence or absence of one of the solvents indicated. Reactions of hydroxyl compounds with alkyl isocyanates, e.g. in the presence of a base such as pyridine, yield the corresponding urethanes.

The compounds of formula I can possess one or more centres of asymmetry. When prepared, they can therefore be obtained as racemates or else in the optically active form if optically active starting materials are used. When synthesized, compounds possessing two or more centres of asymmetry are generally obtained as mixtures of racemates, from which the individual racemates can be isolated in the pure form, for example by recrystallization from inert solvents. If desired, the racemates obtained can be mechanically or chemically resolved into their optical antipodes by methods known per se. Preferably, diastereoisomers are formed from the racemate by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids such as the D and L forms of tartaric acid, dibenzoyltartaric acid, diacetyltartaric acid, camphorsulphonic acids, mandelic acid, malic acid or lactic acid. The different forms of the diastereoisomers can be resolved in a manner known per se, e.g. by fractional crystallization, and the optically active compounds of formula I can be liberated from the diastereoisomers in a manner known per se.

A base of formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce biocompatible salts are suitable for this reaction. Thus it is possible to use inorganic acids, e.g. sulphuric acid, hydrohalic acids such as hydrochloric

acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulphamic acid, as well as organic acids, i.e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulphonic or sulphuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic or ethanesulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemonosulphonic and naphthalenedisulphonic acids and laurylsulphuric acid.

If desired, the free bases of formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate.

The invention further relates to the use of the compounds of formula I and their biocompatible salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of formula I and/or one of their biocompatible salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets,

coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of formula I and their biocompatible salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases, especially parkinsonism, extrapyramidal disorders in neuroleptic therapy, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with α-methyldopa). The compounds can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation and in general as prolactin inhibitors, and also for the therapeutic treatment of cerebral disorders (e.g. migraines), especially in geriatrics in a manner similar to certain ergot alkaloids.

In these treatments, the substances of the invention are normally administered analogously to known, commercially available preparations (e.g. bromocriptine, dihydroergocornin), preferably in dosages of between about 0.2 and 500 mg, especially of between 0.2 and 50 mg per dosage unit. The daily dosage is preferably between about 0.001 and 10 mg/kg of body weight. The low dosages (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use

as anti-migraine preparations; dosages of between 10 and 50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulphate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C. IR = principal bands in the IR spectrum (KBr). MS = peaks in the mass spectrum. Rf values were obtained by thin layer chromatography on silica gel.

Example 1

A solution of 26.6 g of 3-(4-chlorobutyl)indol-5-yl-urea [obtainable by reacting 5-nitroindole with 4-chlorobutyryl chloride to give 3-(4-chlorobutyryl)-5-nitroindole, reduction with diborane to 3-(4-chlorobutyl)-5-nitroindole, hydrogenation to 3-(4-chlorobutyl)-5-aminoindole and reaction with KCNO] and 16 g of 4-phenyl-1,2,3,6-tetrahydropyridine in 200 ml of acetonitrile is stirred for 12 hours at 20° and worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea dihydrate, m.p. 158° (decomposition).

The following are obtained analogously from the appropriate starting materials of formulae II and III:
3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-nitroindole, m.p. 148-150°,
3-[4-(4-p-methoxyphenyl-1,2,3,6-tetrahydropyrid-1-

yl)butyl]indol-5-yl-urea,
3-[4-(4-(3,4-dimethoxyphenyl)-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea,
3-[4-(4-(3,4-methylenedioxyphenyl)-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea,
3-[4-(4-(thien-2-yl)-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea,
3-[4-(4-(thien-3-yl)-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea,
3-[2-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]indol-5-yl-urea,
3-[3-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)propyl]indol-5-yl-urea and
3-[5-(phenyl-1,2,3,6-tetrahydropyrid-1-yl)pentyl]indol-5-yl-urea.

Example 2

A mixture of 2.46 g of 3-(4-aminobutyl)indol-5-yl-urea [obtainable from indol-5-yl-urea via 3-(4-chlorobutyryl)indol-5-yl-urea, 3-(4-chlorobutyl)indol-5-yl-urea and 3-(4-phthalimidobutyl)indol-5-yl-urea] and 2.15 g of 1,5-dichloro-3-phenylpent-2-ene in 40 ml of acetone and 40 ml of water is boiled for 24 hours and worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea dihydrate, m.p. 158° (decomposition).

Example 3

A suspension of 40.7 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-4-oxo-2-thiabutyl]-5-nitroindole [obtainable from 4-(5-nitroindol-3-yl)-3-thiabutyric acid and 4-phenyl-1,2,3,6-tetrahydropyridine] in 3 l of absolute THF is added dropwise, with stirring, to a suspension of 11.7 g of $LiAlH_4$ in 1000 ml of absolute THF and the mixture is decomposed with water and sodium hydroxide solution and worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2- thia-

butyl]-5-nitroindole hydrochloride, m.p. 157-158°. (The nitro group is not attacked by the reducing agent!)

Example 4

1 g of $NaBH_4$ in 20 ml of water is added, with stirring, to a solution of 4.65 g of 1-[4-(5-ureidoindol-3-yl)butyl]-4-phenylpyridinium bromide [obtainable from 3-(4-bromobutyl)indol-5-yl-urea and 4-phenylpyridine] in 50 ml of 1 N NaOH and the mixture is then stirred for a further 3 hours at 60°. After working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-butyl]indol-5-yl-urea dihydrate, m.p. 158° (decomposition), is obtained.

Example 5

4.68 g of 1-benzenesulphonyl-3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea [obtainable from 1-benzenesulphonyl-3-(4-chlorobutyl)indol-5-yl-urea and 4-phenyl-1,2,3,6-tetrahydropyridine] are boiled with 1 g of KOH in 7 ml of water and 14 ml of ethanol for 16 hours and the mixture is worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea dihydrate, m.p. 158° (decomposition).

Example 6

2.76 g of Na are dissolved in 180 ml of ethanol, 21.9 g of 1-(2-mercaptoethyl)-4-phenyl-1,2,3,6-tetrahydropyridine and 23.2 g of 5-ureidogramine are added, the mixture is boiled for 16 hours and evaporated and the residue is worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-indol-5-yl-urea, m.p. 158° (decomposition).

Example 7

A mixture of 26.9 g of 5-ureidogramine hydrochloride, 29.8 g of S-[2-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)ethyl]isothiuronium chloride and 200 ml of 1.5 N aqueous sodium hydroxide solution is stirred for 4 hours at 40°. After working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]indol-5-yl-urea, m.p. 158° (decomposition), is obtained.

3-[4-(4-Phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-aminoindole, Rf 0.18 in toluene/methanol/triethylamine (8:2:1), is obtained analogously with 5- aminogramine dihydrochloride.

Example 8

4.07 g of 3-[4-(4-hydroxy-4-phenylpiperid-1-yl)-butyl]-5-nitroindole [obtainable by reacting 3-(4-bromobutyl)-5-nitroindole with piperid-4-one, followed by reaction with C_6H_5Li and hydrolysis] are stirred with 40 ml of 2 N hydrochloric acid for 2 hours at 50° and the mixture is worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-nitroindole, m.p. 148-150°.

Example 9

0.24 g of NaH (80% suspension in mineral oil) is added to a solution of 3.46 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-hydroxyindole in 35 ml of DMF and the mixture is stirred for 1 hour at 20°. A solution of 0.94 g of chloroacetamide in 10 ml of DMF is then added, the mixture is heated for 2 hours at 50°, with stirring, and evaporated and the residue is worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-carbamoylmethoxyindole, m.p. 94-96°. Methanesulphonate, m.p. 193-195°.

The following are obtained analogously:
3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-

methylcarbamoylmethoxyindole,
3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-dimethylcarbamoylmethoxyindole hydrochloride, m.p. 211° (decomposition), and
3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-ethoxycarbonylmethoxyindole, Rf 0.56 (CH_2Cl_2/CH_3OH, 9:1).

Example 10

1.01 g of N-methylmorpholine are added to a solution of 3.74 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-carboxylic acid in 50 ml of DMF. A solution of 0.61 g of 2-aminoethanol in 5 ml of DMF, 1.35 g of 1-hydroxybenztriazole and a solution of 1.92 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in 20 ml of DMF are added, with stirring. The mixture is stirred for 16 hours at 20° and the filtrate is evaporated. After working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-indole-5-carboxylic acid N-(2-hydroxyethyl)amide, m.p. 168-170°, is obtained.

The following derivatives of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-carboxylic acid are obtained analogously with the appropriate amines:
N-(3-hydroxypropyl)amide, m.p. 154-158°,
N-(4-hydroxybutyl)amide,
N-(1,1-dimethyl-2-hydroxyethyl)amide, IR: 3419, 3265, 2927, 1638, 1620, 1579, 1522, 1471, 1448, 1368, 1308, 1129, 1061, 995, 963, 907, 857, 747, 693,
N-(2-hydroxyethyl)-N-methylamide, m.p. 142-145°,
N,N-bis(2-hydroxyethyl)amide, MS: 462, 444, 399, 375, 357, 327, 285, 257, 227, 198, 164, 158, 129, 105, 88, 74,
N-(2-methoxyethyl)amide, m.p. 143-144°,
N-(2-acetoxyethyl)amide,
N-(2-benzoyloxyethyl)amide, MS: 399, 341, 241, 213, 173, 158, 122, 105, 91, 77,
N-(methoxycarbonylmethyl)amide, m.p. 145-147°,
N-(ethoxycarbonylmethyl)amide, m.p. 169°,

N-(carbamoylmethyl)amide hydrate, m.p. 183-185°,
N-(2-sulphoethyl)amide, m.p. 159-160°,
N-(2-dimethylaminoethyl)amide, IR: 3417, 3240, 1632, 1578, 1535, 1495, 1466, 1445, 1375, 1304, 1244, 1185, 1128, 1097, 1034, 961, 908, 817, 747, 693,
anilide,
p-fluoroanilide, m.p. 167-168°,
N-benzylamide, m.p. 155-156°,
N-benzyl-N-methylamide, IR: 3420, 3238, 3028, 2930, 2713, 1620, 1608, 1579, 1495, 1446, 1401, 1358, 1250, 1193, 1094, 1076, 1027, 1001, 817, 747, 697,
N-(2-morpholinoethyl)amide, m.p. 153-154°,
N-[2-(pyrid-2-yl)ethyl]amide, m.p. 148-149°,
pyrrolidide dihydrochloride, m.p. 188-190° (decomposition),
piperidide, m.p. 94-95°,
morpholide dihydrochloride, IR: 3415, 3227, 2925, 2858, 2710, 2588, 1621, 1495, 1440, 1386, 1362, 1329, 1273, 1248, 1192, 1156, 1113, 1068, 1023, 942, 920, 840, 819, 749, 606,
4-methylpiperazide, IR: 3419, 3226, 3031, 2933, 2856, 2792, 1625, 1604, 1494, 1451, 1440, 1366, 1294, 1255, 1234, 1172, 1139, 1071, 1050, 1023, 964, 925, 892, 747, 693,
4-phenylpiperazide, IR: 3412, 3231, 3038, 3002, 2919, 2854, 2765, 1626, 1593, 1565, 1479, 1457, 1434, 1377, 1311, 1281, 1238, 1160, 1132, 1098, 1052, 1014, 980, 945, 864, 813, 772, 747, 694,
4-(pyrimidin-2-yl)piperazide dihydrochloride, m.p. 235-236° (decomposition),
4-(5-methylthiazol-2-yl)piperazide dihydrochloride, m.p. 211-213° (decomposition),
4-p-fluorobenzoylpiperazide, m.p. 143-145°,
4-ethoxycarbonylpiperazide, m.p. 115-119° (decomposition),
4-(carbamoylmethyl)piperazide,
4-(N-isopropylcarbamoylmethyl)piperazide dihydrochloride, m.p. 156° (decomposition),
4-(N,N-dimethylcarbamoylmethyl)piperazide,

4-pyrrolidinocarbonylmethylpiperazide, MS: 553, 457, 441, 394, 357, 327, 296, 227, 198, 155, 151, 129, 115, 91, 70, 56, 42,
4-dimethylaminopiperidide dihydrochloride dihydrate, decomposition above 105°,
4-p-fluorobenzamidopiperidide, m.p. 110° (decomposition),
4-ethoxycarbonylpiperidide, m.p. 117-119°,
4-carbamoylpiperidide, m.p. 93-98°,
4-p-chlorophenylpiperidide, IR: 3422, 3236, 3020, 2928, 2854, 1643, 1602, 1493, 1445, 1369, 1320, 1297, 1276, 1231, 1130, 1090, 1033, 1014, 826, 747, 694,
4-piperidinopiperidide dihydrochloride, Rf 0.15 (methylene chloride/methanol/ethyl acetate 7:2:1),
4-morpholinopiperidide dihydrochloride hydrate, m.p. 90° (decomposition), and
4-phenyl-1,2,3,6-tetrahydropyridide hydrochloride, m.p. 88-89°.

The following derivatives of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-oxyacetic acid are obtained analogously:
N-(ethoxycarbonyl)amide hydrochloride, m.p. 191-193°, and
N-(1-ethoxycarbonyl-2-hydroxyethyl)amide hydrochloride, m.p. 118-120°.

Example 11

HCl is passed into a solution of 3.55 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-cyanoindole and 1.5 g of thioacetamide in 40 ml of DMF until saturation is reached, and the mixture is boiled for 30 minutes. It is evaporated and the residue is worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-thiocarboxamide, decomposition at 118°.

Example 12

6 ml of 30% H_2O_2 are added to a boiling solution of 3.93 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-

yl)-2-thiabutyl]-5-nitroindole in 50 ml of ethanol and the mixture is then boiled for 3 hours. After the addition of a further 4 ml of 30% H_2O_2, the mixture is boiled for another 9 hours, cooled and worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-nitroindole S-oxide.

Example 13

9 ml of 30% H_2O_2 are added to a solution of 3.93 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-nitroindole in 20 ml of acetic acid and the mixture is boiled for 90 minutes. After working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-nitroindole S,S-dioxide, Rf 0.7 (acetone), is obtained.

Example 14

A mixture of 4.05 g of 3-[4-(4-p-methoxyphenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-nitroindole, 3.5 g of pyridine hydrochloride and 80 ml of pyridine is boiled for 3 hours. It is cooled and evaporated and the residue is worked up in conventional manner to give 3-[4-(4-p-hydroxyphenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-nitroindole.

Example 15

9.3 g of $SnCl_2$ are added, with stirring, to a suspension of 3.75 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-nitroindole in 45 ml of concentrated hydrochloric acid and 30 ml of ethanol and the mixture is then boiled for 0.5 hour. It is poured on to ice and worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-aminoindole, m.p. 113°.

Example 16

A mixture of 2 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-aminoindole, 2 ml of acetyl chloride and 15 ml of triethylamine is stirred for 16 hours at 20°. After working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-acetamidoindole, m.p. 172-173°, is obtained.

The following are obtained analogously by acylation:

3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-acetamidoindole,

3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-benzamidoindole,

3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-methylsulphonamidoindole,

3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-benzamidoindole and

3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]-5-methylsulphonamidoindole, m.p. 181-183°.

Example 17

A mixture of 4.17 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-carboxylic acid N-(2-hydroxyethyl)amide, 1.41 g of benzoyl chloride and 50 ml of triethylamine is stirred for 2 hours at 20°. After evaporation and working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-carboxylic acid N-(2-benzoyloxyethyl)amide is obtained.

Example 18

A mixture of 4.17 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-carboxylic acid N-(2-hydroxyethyl)amide, 0.65 g of methyl isocyanate and 40 ml of pyridine is stirred for 16 hours at 20°. After evaporation and working-up in conventional manner, 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-

carboxylic acid N-(2-N-methylcarbamoyloxyethyl)amide, m.p. 117-118°, is obtained.

Example 19

4.32 g of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]-5-ethoxycarbonylmethoxyindole are boiled for 2 hours with 20 ml of water and 100 ml of 2 N ethanolic KOH and the mixture is worked up in conventional manner to give 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-butyl]indol-5-oxyacetic acid hydrochloride, decomposition above 175° (sinters at 132°).

The following Examples relate to pharmaceutical preparations containing amines of formula I or their acid addition salts:

Example A: Tablets

A mixture of 1 kg of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indole-5-carboxylic acid N-(2-hydroxyethyl)amide, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to tablets in conventional manner so that each tablet contains 10 mg of active ingredient.

Example B: Coated tablets

Tablets are formed by compression analogously to Example A and then covered in conventional manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example C: Capsules

2 kg of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-2-thiabutyl]indol-5-yl-urea are filled into hard gelatin capsules in conventional manner so that each capsule contains 20 mg of the active ingredient.

Example D: Ampoules

A solution of 1 kg of 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)butyl]indol-5-yl-urea dihydrate in 60 l of double-distilled water is filtered under sterile conditions, filled into ampoules and lyophilized under sterile conditions and the ampoules are sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Tablets, coated tablets, capsules and ampoules containing one or more of the other active ingredients of formula I and/or their biocompatible acid addition salts can be obtained analogously.

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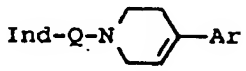
6100 D a r m s t a d t

Claims

1. An indole derivative of formula I



I

wherein
Ind is an indol-3-yl radical substituted by $-O-CH_2-CO-R^1$, $-NHR^2$, $-NO_2$, $-CO-NR^3R^4$ or $-CSNH_2$,
R^1 is OH, OA, NH_2, NHA, NA_2, $NH-CH_2COOA$ or $NHCH(CH_2OH)COOA$,
R^2 is H, Ac, $CONH_2$, CONHA, $CONA_2$ or SO_2A,
R^3 is H, A or hydroxyalkyl,
R^4 is hydroxyalkyl, AO-alkyl, AcO-alkyl, ANH-CO-O-alkyl, AOOC-alkyl, H_2NCO-alkyl, HSO_3-alkyl, A_2N-alkyl, Ar, Ar-alkyl or Het-alkyl,
R^3 and R^4 together are also an alkylene group having 3-7 C atoms, which can be interrupted by O or NR^5 and/or substituted by NA_2, NHAc, COOA, $CONH_2$, Ar or Het, and/or can contain an additional double bond,
R^5 is H, A, Ar, Het, Ac, COOA, CH_2CONH_2, CH_2CONHA, CH_2CONA_2 or CH_2CONR^6,
R^6 is alkylene having 3-7 C atoms,
Q is $-(CH_2)_n-$, $-CH_2-S-CH_2CH_2-$, $-CH_2-SO-CH_2CH_2-$ or $-CH_2-SO_2-CH_2CH_2-$,
n is 2, 3, 4 or 5,
A is alkyl having 1-4 C atoms,
-alkyl- is alkylene having 1-4 C atoms,
Ar is a phenyl group which is unsubstituted, monosubstituted or disubstituted by F, Cl, Br, OA and/or OH or substituted by a methylenedioxy group, or a thien-2-yl or thien-3-yl group,

Ac is A-CO- or Ar-CO- and
Het is a saturated or unsaturated 5-membered or 6-membered heterocyclic radical having 1-4 N, O and/or S atoms, which can be fused with a benzene ring and/or monosubstituted or disubstituted by A,
and its salts.

2. a) 3-[4-(4-Phenyl-1,2,3,6-tetrahydropyrid-1-yl)-butyl] indole-5-carboxylic acid N-(2-hydroxy-ethyl)amide;
b) 3-[4-(4-phenyl-1,2,3,6-tetrahydropyrid-1-yl)-butyl]indol-5-yl-urea.

3. A process for the preparation of indole derivatives of formula I according to Claim 1, and their salts, characterized in that a compound of formula II

$$Ind\text{-}Q\text{-}X^1 \qquad II$$

wherein
X^1 is X or NH_2,
X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and
Ind and Q are as defined,
is reacted with a compound of formula III

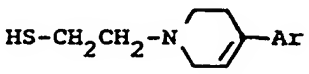
$$X^2\text{-}CH_2CH_2CAr{=}CH\text{-}CH_2X^3 \qquad III$$

wherein
X^2 and X^3 can be identical or different and are each X if $X^1 = NH_2$ or are together NH in other cases, and
Ar is as defined,
or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds is treated with a reducing agent,
or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolyzable groups is treated with a solvolyzing agent,

or in that, to prepare thioethers of formula I in which Q is $-CH_2-S-CH_2CH_2-$, a compound of formula IV

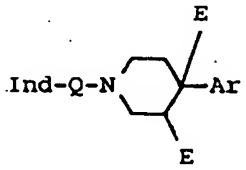
$$Ind-CH_2N(R)_2 \qquad IV$$

wherein
R is alkyl having 1-4 C atoms or else both radicals R together are $-(CH_2)_p-$ or $-CH_2CH_2OCH_2CH_2-$,
p is 4 or 5 and
Ind is as defined,
is reacted with a thiol of formula V



V

wherein
Ar is as defined,
or with one of its reactive derivatives,
or in that a compound of formula VI



VI

wherein
one of the radicals E is X, CN or NH_2,
the other radical E is H and
Ind, Q, Ar and X are as defined,
is treated with an agent which eliminates HE,
or in that, to prepare a compound of formula I in which Ind is an indol-3-yl radical substituted by $-O-CH_2-CO-R^1$, a hydroxyindole which has formula I except that Ind has been replaced by an indol-3-yl radical substituted by an OH group, or one of its reactive derivatives, is reacted with a compound of the formula $X-CH_2-CO-R^1$ (wherein X and R^1 are as defined),
or in that, to prepare a compound of formula I in which

Ind is an indol-3-yl radical substituted by $-CO-NR^3R^4$, an indolecarboxylic acid which has formula I except that Ind has been replaced by an indol-3-yl radical substituted by a COOH group, or one of its reactive derivatives, is reacted with a compound of the formula HNR^3R^4 (wherein R^3 and R^4 are as defined),
or in that, to prepare a compound of formula I in which Ind is an indol-3-yl radical substituted by $-CS-NH_2$, a cyanoindole which has formula I except that Ind has been replaced by an indol-3-yl radical substituted by a CN group is reacted with H_2S or an agent which releases H_2S, and/or in that, if desired, in a compound of formula I, a thioether group is oxidized to an SO group or SO_2 group or an SO group is oxidized to an SO_2 group, and/or an OA group is cleaved to form an OH group, and/or an Ind group is converted into another Ind group, and/or in that a resulting base of formula I is converted into one of its salts by treatment with an acid or base.

4. A process for the manufacture of pharmaceutical preparations, characterized in that a compound of formula I and/or one of its biocompatible salts are converted into a suitable dosage form together with at least one solid, liquid or semiliquid excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

5. A pharmaceutical preparation, characterized in that it contains at least one compound of general formula I and/or one of its biocompatible salts.

6. Use of compounds of formula I according to Claim 1, or their biocompatible salts, for the manufacture of a drug.

7. Use of compounds of formula I according to Claim 1, or their biocompatible salts, for controlling diseases.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente